REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Final Office Action mailed on December 20, 2007. Previously, claim 1 had been cancelled and claims 2-25 had been examined. By entry of this amendment, claims 2-7, 10, and 14-25 have been cancelled without prejudice or disclaimer, claims 8-9 and 11-13 have been amended, and claims 26-34 have been added. No new matter has been added.

Specifically, claims 8 and 9 have been amended to indicate that "the knockout bacteria more efficiently produce 1,3-propanediol and 3-hydroxypropionic acid compared to *Lactobacillus reuteri* that do not lack glycerol dehydrogenase activity." Support for amendments to claims 8 and 9 can be found in the specification, for example, at least at original claim 10 and Example 9. Claim 11 has been amended to incorporate subject matter from now cancelled claims 2-5, 14, 16, 18, 20, and 22. Support for amendments to claim 11 can be found in the specification, for example, at least at original claims 2-5 and paragraphs [0021]-[0029], [0039]-[0042], [0046]-[0049], [0054]-[0059], and [0072]-[0074]. Claims 12-13 have been amended to specify "1,3-propanediol and 3-hydroxypropionic acid" instead of "1,3-propanediol and/or 3-hydroxypropionic acid." Support for that amendment can be found in the specification, at least at Example 7. Thus, the amendments to the pending claims are fully supported by the application as filed.

As noted above, claims 26-34 have been added and find support as follows:

> New claim 30 includes subject matter from now cancelled claims 2-5, 15, 17, 19, 21, and 23. Support for claim 30 can be found in the specification, for example, at least at original claim 1 and paragraphs [0030]-[0038], [0043]-[0045], [0050]-[0053], [0060]-[0065], and [0075]-[0077].
>
> New claims 26 and 31 depend from independent claims 11 and 30, respectively, and include subject matter from now cancelled claim

6. Support for those claims is found in the specification, for example, at least at original claim 6 and paragraph [0070].

New claims 28 and 32 depend from claims 26 and 31, respectively, and include subject matter from now cancelled claim 7. Support for those claims is found in the specification, for example, at least at original claim 7 and paragraph [0071].

New claims 29 and 34 depend from claims 11 and 30, respectively, and include subject matter from now cancelled claim 10. Support for those claims can be found in the specification, at least at original claim 10 and paragraphs [0177]-[0185].

New claim 27 includes subject matter from now cancelled claim 24. Support for claim 27 is found in the specification, for example, at least at paragraphs [0078]-[0080].

New claim 33 includes subject matter from now cancelled claim 25. Support for claim 33 can be found in the specification, for example, at least at paragraphs [0081]-[0083]. Thus the newly added claims find full support in the specification.

Upon entry of the present amendment, claims 8-9, 11-13, and 26-34 will be pending.

Preliminary Matters

Applicants thank the Examiner for confirming the claims for priority. Applicants note with appreciation the Examiner's withdrawal of the prior rejection of claims 1-7 and 10 under 35 U.S.C. § 112, second paragraph; claims 1-10 under 35 U.S.C. § 112, first paragraph (written description); claims 1-7 and 10 under 35 U.S.C. § 112, first paragraph (lack of enablement); claims 1-5 and 10 under 35 U.S.C. § 102(b); and claims 1 and 10 under 35 U.S.C. § 102(b); and claims 1-10 under 35 U.S.C. § 103(a).

Claim Objections

Claims 2-10 were "objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim." Final Office Action at page 5, emphasis in original.

Applicants note that claims 8 and 9 are independent claims; accordingly, they do not depend from any other claim. Applicants have cancelled claims 2-7 and 10. Thus, this objection is moot with respect to those claims. Applicants do note that the new dependent claims limit the subject matter of a previous claim. Applicants respectfully request the withdrawal of the objection.

Claim Rejections

I. Rejection of claims 11 and 14-25 under 35 U.S.C. § 112, First Paragraph

Claims 11 and 14-25 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, "there is considerable breadth to the sequences which are encompassed by the instant claims" because genes are "defined by homology through hybridization or as a sequence derived from deletion, substitution or addition of amino acids." Action at page 7. The Examiner concluded that "in view of the potentially large numbers of organisms comprising genetic mutations of polynucleotides encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed." *Id.* at page 9.

Applicants respectfully traverse. As noted above, claims 14-25 have been cancelled. Thus, this rejection with respect to claims 14-25 is moot. Claim 11, as amended, encompasses introduced genes that encode proteins comprising amino acid sequences identified by specific SEQ ID NOs. Similarly, new claim 30 encompasses various introduced genes comprising specific nucleotide sequences identified by SEQ ID NOs. Neither of those independent claims define genes by homology through hybridization or as sequences derived from deletion, substitution, or addition of amino acids. Accordingly, the skilled person would immediately

recognize that Applicants were in possession of this claimed genus. Therefore, Applicants respectfully request withdrawal of the rejection.

II. Rejection of claim 11 under 35 U.S.C. § 102(b)

Claim 11 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ahrne et al. (Current Microbiology, 1992, Vol. 24: 199-205). The Examiner stated that the transformation system of Ahrne anticipates claim 11 because "all of the enzymes described in claim 11 are intrinsic to the organism, *Lactobacillus reuteri*." Action at page 10.

Applicants respectfully traverse. According to the M.P.E.P., "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 at 2100-67 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Here, Ahrne does not teach or suggest each and every element of claim 11. Specifically, Ahrne does not teach or suggest a transformant of *Lactobacillus reuteri* comprising the introduced genes recited in claim 11. Instead, Ahrne simply outlines an electroporation transformation system for *Lactobacillus reuteri*. Thus, Ahrne does not anticipate the instant claims. Applicants respectfully request withdrawal of the rejection.

III. Rejection of claims 10-11 and 2-7 under 35 U.S.C. § 102(e)

Claims 10-11 and 2-7 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Laffend et al. (US 7,135,309, issued November 14, 2006). The Examiner relied on Laffend for teaching that "1,3-propanediol can be produced from the fermentation of glycerol . . . in . . . Lactobacillus." Action at page 11. Quoting Laffend, the Examiner stated that "cells suitable for [Laffend's] invention comprise those that harbor a dehydratase enzyme . . .

[t]ypically the enzyme will be either a glycerol dehydratase or a diol dehydratase . . . includ[ing] mutated or recombinant organisms belonging to the genera *Lactobacillus*." *Id.*

Applicants respectfully traverse. As noted above, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 at 2100-67 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987))." Although Laffend discusses production of 1,3-propanediol, Laffend does not teach or suggest a transformant of *Lactobacillus reuteri* comprising the specific introduced genes recited in claim 11. Specifically, Laffend does not disclose a transformant comprising genes introduced from *Lactobacillus reuteri* encoding the large, medium, and small subunits of glycerol dehydratase; large and small subunits of a reactivation factor for glycerol dehydratase; propionaldehyde dehydrogenase; and propanol dehydrogenase. Thus, Laffend does not anticipate the current claims. Applicants respectfully request withdrawal of the rejection.

IV. Rejection of claims 2-7 and 10-11 under 35 U.S.C. § 103(a)

Claims 2-7 and 10-11 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Skraly et al. (US 6,329,183, issued December 11, 2001), in view of Dobrogosz et al. (US 5,352,586, issued October 4, 1094). The Examiner relied on Skraly for teaching that "all the genes necessary to implement the productions of poly(3-hydroxypropionate) from central metabolic intermediates via glycerol have been cloned and are available in genetically manipulatable for[m,] any combination of plasmid-borne and integrated genes may be used." *Id.* at page 15. The Examiner, however, did acknowledge that Skraly "does not teach the source of the genes cited in claims 2-5 as coming from *Lactobacillus reuteri*." *Id.*

The Examiner relied on Dobrogosz for teaching "*Lactobacillus reuteri* comprising the genes for glycerol dehydratase" and "culturing *Lactobacillus reuteri* in glycerol to produce 1,3-propanediol and/or β-hydroxypropionic acid." Action at page 14. The Examiner also indicated that "[t]he genes for propanol dehydrogenase, propionaldehyde dehydrogenase, propionate kinase, and 1,3-propanediol oxidioreductase are intrinsic the microorganism." *Id.*

According to the Examiner, "it would have been obvious to the person or ordinary skill in the art at the time the invention was made to culture recombinant bacteria in glycerol to produce 1,3-propanediol and/or 3-hydroxypropionic acid, using a variety of possible enzymatic alternatives in a variety of possible microorganisms." *Id.* at page 15. The Examiner then urged that one of skill in the art "would have been motivated to make those modification because 1,3-propanediol and/or 3-hydroxypropionic acid are 'industrially useful as polymers or as starting materials for a range of chemical intermediates.'" *Id.* at page 16 (quoting Skraly, abstract). The Examiner further stated that there was a reasonable expectation of success because Skraly and Dobrogosz "teach production of 1,3-propanediol and/or β-hydroxypropionic acid." *Id.*

Applicants respectfully traverse. As a preliminary matter, Applicants point out that claims 2-7 and 10 have been cancelled. Thus, this rejection with respect to those claims is moot.

The Supreme Court recently reaffirmed the framework set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) for applying the statutory language of 35 U.S.C. § 103:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id., at 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545.*

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734 (2007), quoting *Graham*, 383 U.S. at 17-18. The Supreme Court further explained that "the factors continue to define the inquiry that controls." *Id.*

The *Graham* test reinforces Applicants' assertion that the claims are not obvious. First, Skraly does not teach or suggest a transformant of *Lactobacillus reuteri* particularly comprising genes introduced from *Lactobacillus reuteri* encoding large, medium, and small subunits of glycerol dehydratase; large and small subunits of a reactivation factor for glycerol dehydratase; propionaldehyde dehydrogenase; and propanol dehydrogenase, comprising the SEQ ID NOs specified in the claims. Although Skraly does state that "[m]any different implementation [for producing poly(3-hydroxypropionate)] will be apparent to those skilled in the art" at col. 5, lines 45-46, this sweeping statement does not suggest that any particular combination of genes would be useful, let alone the claimed combination of genes introduced from *Lactobacillus reuteri.* Thus, Skraly cannot suggest the claimed *Lactobacillus reuteri* transformant comprising the selection of introduced genes.

Dobrogosz does not cure the above-mentioned deficiency of Skraly. For example, unlike the instant application, Dobrogosz does not teach or suggest the need for a "transformant." Dobrogosz does teach "biologically pure strains of *L. reuteri.*" Col. 4, lines 3-4. Specifically, Dobrogosz states that Lactobacillus strain 208-A "carries out an anaerobic dehydration (involving glycerol dehydratase) of 2 moles of glycerol yielding 2 moles of β-hydroxypropion-aldehyde which in turn is dismutated to 1 mole of β-hydroxypropionic acid and 1 mole of 1,3-propanediol." Dobrogosz at col. 2, lines 61-65. In contrast to Lactobacillus strain 208-A, the instant transformants comprise genes introduced from *Lactobacillus reuteri.* Furthermore, the specification states that "[t]ransformants can be obtained by ligating the 4 aforementioned types

of genes or parts thereof to an adequate vector and introducing the resulting recombinant vector into a host so as to allow the gene of the present invention to express therein." Specification at paragraph [0120]. Thus, the transformants of the instant invention are generated using recombinant biology techniques. Such transformants are not "biologically pure strains."

The fact that the genes encoding large, medium, and small subunits of glycerol dehydratase; large and small subunits of a reactivation factor for glycerol dehydratase; propionaldehyde dehydrogenase; and propanol dehydrogenase are intrinsic to *L. reuteri* does not suggest a transformant comprising those particular introduced genes, as opposed to the many other genes that are intrinsic to *L. reuteri*. Accordingly, Dobrogosz does not suggest any transformant with the claimed combination of introduced genes from *L. reuteri*.

Regarding motivation, the Examiner stated that one of skill in the art "would have been motivated to make those modification because 1,3-propanediol and/or 3-hydroxypropionic acid are 'industrially useful as polymers or as starting materials for a range of chemical intermediates.'" Action at page 16 (quoting Skraly, abstract). According to the Federal Circuit, "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). Despite the fact that 1,3-propanediol and/or 3-hydroxypropionic acid may be industrially important, neither Skraly nor Dobrogosz suggests the desirability of a transformant comprising the indicated introduced genes. Therefore, one skilled in the art would have no reason to combine Skraly and Dobrogosz.

Based on the above analysis, the combination of Skraly and Dobrogosz do not suggest all of the claimed elements of claim 11 or its parallel claim, claim 30. For at least this reason, the

Examiner has not established a *prima facie* case of obviousness. Applicants, therefore, respectfully request the withdrawal of this rejection.

V. Rejection of claims 8-9 and 12-13 under 35 U.S.C. § 103(a)

Claims 8-9 and 12-13 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nair et al. (US 7,005,291, issued February 28, 2006). Regarding claims 8-9, the Examiner stated that Nair teaches a "recombinant host having disruptions in genes encoding endogenous glycerol dehydrogenase enzymes." Action at page 17. According to the Examiner, "*Lactobacillus reuteri* inherently contains the [p]hosphate acetyltransferase gene and pdu operon." *Id.* Regarding claims 12 and 13, the Examiner stated that Nair teaches a "process . . . for a recombinant organism . . . in a host cell having disruptions in the endogenous . . dehydrogenase genes . . . [a]pplicant's process may generally [be] applied to the production [of] compounds where glycerol is a key intermediate, e.g., 1,3-propanediol." *Id.* The Examiner alleged that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the teachings of Nair et al. to generate a *Lactobacillus reuteri* comprising a knocked out phosphotransacylase gene in order to produce compounds where glycerol is the key intermediate." *Id.* The Examiner also alleged that the "combination [of prior art elements] would have yielded predictable results." *Id.* The Examiner then concluded that "[e]ach of the elements (recombinant microorganisms comprising [a] knocked out phosphotransacylase gene; recombinant production of 1,3-propanediol by [a] recombinant host having disruptions in genes encoding endogenous glycerol dehydrogenase enzymes) are taught by Nair." *Id.* at pages 17-18.

Applicants respectfully traverse. Applicants first point out that contrary to the Examiner's contentions, the claims do not recite a "recombinant organism comprising [a]

knocked out phosphotransacylase gene." Instead, claim 9 expressly provides that the knockout bacteria comprises a gene encoding phosphotransacylase. Applicants respectfully request that the Examiner clarify the statements regarding *Lactobacillus reuteri* comprising a knocked out phosphotransacylase gene. By not further responding to those statements, Applicants in no way acquiesce to the Examiner's contentions.

The Examiner has not established that Nair or any other alleged prior art documents teach or suggest all of the claim limitations. Specifically, the Examiner has not pointed to any document suggesting that "[glycerol dehydrogenase] knockout bacteria more efficiently produce 1,3-propanediol and 3-hydroxypropionic acid compared to *Lactobacillus reuteri* that do not lack glycerol dehydrogenase activity," as recited by claims 8 and 9. Nair is in fact completely silent on glycerol dehydrogenase "knockout bacteria [that] more efficiently produce 1,3-propanediol and 3-hydroxypropionic acid compared to *Lactobacillus reuteri* that do not lack glycerol dehydrogenase activity." At most, Nair discloses *E. coli* that lack glycerol dehydrogenase activity. *See* Example 6 at col. 24. However, Nair does not teach or suggest that those *E. coli* or any other bacteria more efficiently produce 1,3-propanediol and 3-hydroxypropionic acid compared to bacteria that do not lack glycerol dehydrogenase activity. Indeed, Nair suggests a completely different method of producing 1,3-propanediol. Nair's method involves culturing bacteria that lack glycerol dehydrogenase activity, but have dehydratase activity and express exogenous genes encoding a protein having a glycerol-3-phosphate dehydrogenase activity and glycerol-3-phosphate phosphatase activity. *See* Nair at col. 15, lines 5-31. One skilled in the art would, therefore, recognize that Nair's disclosure does not teach or suggest the instant claims. Thus, the Examiner has not established a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the rejection.

VI. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 20, 2008

By: Jean Burke Fordis
Jean Burke Fordis
Reg. No. 32,984
Customer No. 22,852